

Prevention of CPT-11 Induced Toxicity by a Chinese Medicinal Formulation, PHY-906

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Abstract

Irinotecan hydrochloride (CPT-11, Camptosar®) is a clinically used anti-cancer agent, whose active metabolite is SN-38. The dose limiting toxicity is severe, delayed-onset diarrhea. This side effect is related to the biliary excretion of SN-38 glucuronide, which can be reactivated by β -glucuronidase of bacteria in intestine to SN-38. A treatment that can decrease the formation of SN-38 in intestine should reduce the toxicity of CPT-11. PHY-906, a traditional Chinese herbal formulation used for thousands of years to treat various gastrointestinal ailments, shows potent inhibitory activity on *E. coli* β -glucuronidase. This formulation, when given orally, was compared with loperamide and other anti-diarrhea Chinese formulations (TJ-14ST, TJ-15, PHY-915) in female BDF-1 mice, bearing colon 38 carcinoma, that were treated with high dose of CPT-11. Only PHY-906 and PHY-915 decreased the toxicity of CPT-11, as measured by the weight lost of mice. However, PHY-915 antagonized the anti-tumor effect of CPT-11 while PHY-906 was shown to enhance the anti-cancer activity. The potent inhibition of β -glucuronidase, decrease of toxicity and enhanced anti-tumor activity of CPT-11 are factors that suggest the PHY-906 should be developed to prevent CPT-11 toxicity.

Effect of Different Herbal Formulations on Cytotoxicity in Different Cell Lines

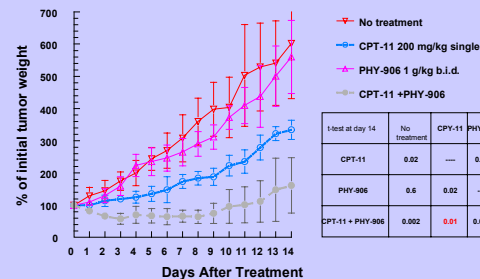
| Herbal Formulation | IC ₅₀ (mg/ml) ^a | | | | |
|-----------------------|---------------------------------------|-------------|-------------|-----------------|-----------------|
| | KB | HepG2 | CEM | HCT116 | Colon 38 |
| PHY-906A | 1.35 ± 0.52 | 0.28 ± 0.17 | 1.45 ± 0.35 | 1.3 | 0.08 |
| PHY-906B ^b | 1.60 ± 0.99 | 0.17 ± 0.12 | 1.29 ± 0.02 | 1.2 | 0.08 |
| PHY-915 | >10 | 7.50 ± 1.29 | >2 | Ng ^c | Ng ^c |
| PHY-14ST | 5.25 ± 2.47 | 5.25 ± 2.47 | >2 | Ng ^c | Ng ^c |
| PHY-15 ST | 2.25 ± 1.77 | 1 | 1.18 ± 0.18 | Ng ^c | Ng ^c |

^aBased on the dry weight of herbal formulation.

^bNg, not determined.

^cDifferent batch of PHY-906A.

Effect of PHY-906 on Antitumor Activity of CPT-11 in HepG-2 Bearing NCr-Nude Mice



Indications for Traditional Use of PHY-906 Formulation

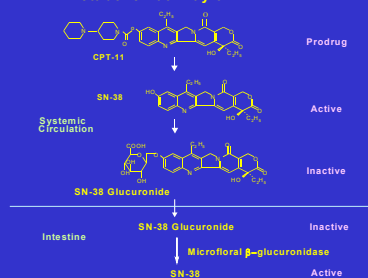
- Diarrhea
- Subcardiac Distention
- Abdominal Spasms
- Fever
- Headache
- Vomiting
- Nausea
- Extreme Thirst

Putative Biological Activities of Individual Herbs in the PHY-906 Formulation

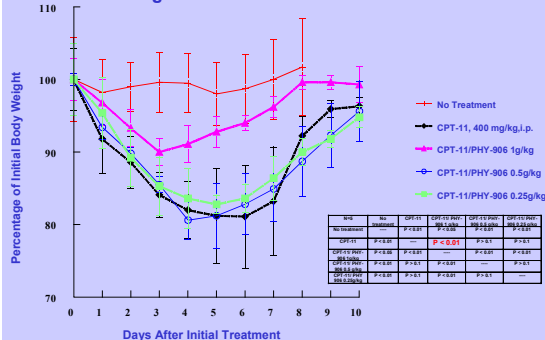
- Anticancer
- Immunomodulation
- Antidiarrhea
- Antibacterial
- Anticoagulation
- Somnolence
- Liver Protection
- Antiviral
- Antiemetics
- Analgesic
- Appetite Improvement

Ref: (1) "Shang Han Lun" of the Han Dynasty
 (2) "Compendium of Materia Medica" (1596), Hong-Yen Hsu and Chou-Shin Hsu, Oriental Healing Arts Institute, California.
 (3) "Chinese Botany" (1992), Shanghai Science and Technology Publishing Company.

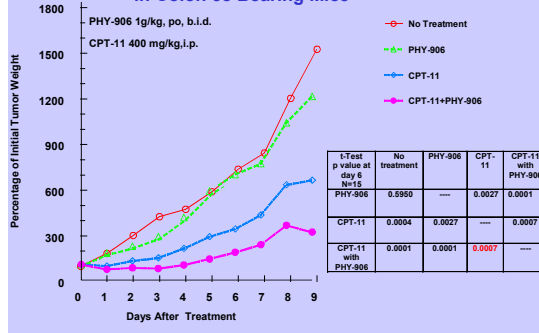
Metabolic Pathway of CPT-11



Effect of PHY-906 on Weight Loss in Tumor Bearing Mice Treated with CPT-11



Effect of PHY-906 on Antitumor Activity of CPT-11 in Colon 38 Bearing Mice



Effect of Different Herbal Formulations on Tumor Bearing Mice Treated with CPT-11

| Herbal Formulation (1 g/kg, bid, 8 days) | Protection from Body Weight Loss | Antitumor Effect | Animal Death (Death/Total) |
|--|-------------------------------------|-------------------------------------|----------------------------|
| None | | | 4 / 24 ^a |
| PHY-906 | Significant (p=0.0044) | Enhancement (p=0.0027) ^b | 0 / 24 (p=0.8416) |
| PHY-14ST | No Change (p=0.1072) ^b | No Change (p=0.2742) ^b | 1 / 10 |
| PHY-15ST | No Change (p=0.3259) ^b | No Change (p=0.6535) ^b | 0 / 3 |
| PHY-915 | Significant (p=0.0030) ^b | Decrease (p=0.0033) ^b | 0 / 5 |
| Loperamide | No Change (p=0.9706) ^b | No Change (p=0.1593) ^b | 3 / 10 |

All of P values were calculated using student paired t-test.
^aCalculated on the day that CPT-11 treated mice reached the maximum body weight loss.
^bCalculated on the day 6 after initial drug treatment.
^cCalculated on the number of dead animal on day 16.

Effect of Different Herbal Formulations on beta-Glucuronidase Inhibition

| Formulation | IC ₅₀ (mg/ml) |
|-----------------------|--------------------------|
| PHY-906A | 0.53 ± 0.25 |
| PHY-906B ^a | 0.5 ± 0.21 |
| TJ-14ST | 2.2 |
| TJ-15ST | 4 |
| PHY-915 | 1.35 ± 0.10 |

^a Different batch of PHY-906A